Claim 7 has been amended to correct an informality, wherein an "antibody" was referred to as an "antibody fragment." The amendment, which merely clarifies the claim language, is supported, for example, at page 18, lines 14-15, and, therefore, does not add new matter.

B. Rejections under 35 U.S.C. § 112

In the Office Action mailed March 30, 2000, claim 7 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite. This rejection is respectfully is traversed.

It was alleged in the Office Action that claim 7 is indefinite in reciting that the "antibody" is an "antibody fragment" because the whole cannot be a fragment of itself. Claim 7 has been amended to more clearly indicate that the "antibody or antigen binding fragment thereof of claim 1" is an "antibody fragment." Accordingly, it is submitted that the claim is clearly defined and, therefore, respectfully requested that this rejection of claim 7 under 35 U.S.C. § 112, second paragraph, be removed.

Also in the Office Action, the specification was objected to and claim 4 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description. The objection and corresponding rejection are respectfully traversed.

It was stated in the Office Action that the specification does not support "an actual human antibody" that is reactive with HBGF because the specification allegedly only discusses human antibodies as *de novo* antibodies with human constant regions, which, it was further alleged, are the same as "humanized" antibodies (Office Action, paragraph bridging pages 2-3). However, the specification clearly refers to both human and humanized antibodies (page 15, lines 5-7). One skilled in the art clearly would have been apprised that both human antibodies and humanized antibodies were contemplated at the time the subject application was filed.

Furthermore, the specification discloses combining, for example, human antibody chains with non-human antibody chains (page 16, lines 11-17), clearly demonstrating that human anti-HBGF antibodies were contemplated at the time the subject application was filed.

With respect to the language cited in the paragraph bridging pages 2 and 3, Applicants note that the disclosure cited by the Examiner in the Office Action is directed to the production of transgenic mice that produce "human" antibodies (page 15, lines 19-23). Such antibodies, which are distinguishable from the human antibodies of claim 4, are referred to as "human" antibodies because they are encoded, for example, by a nucleic acid molecule that is derived from a human and encodes the constant regions, but are produced in the transgenic mouse. As such, this disclosure is separate from the disclosure in the specification of human antibodies as discussed above.

In summary, the specification clearly discloses human and humanized antibodies, such that one skilled in the art would have been apprised of a distinction between these types of antibodies, and further discloses the use, for example, of human variable region domains to produce a "hybrid" antibody, thus demonstrating that human antibodies were contemplated at the time the subject application was filed. Accordingly, it is respectfully requested that this objection to the specification and the corresponding rejection of claim 4 under 35 U.S.C. § 112, first paragraph, be removed.

C. Prior Art Rejections

In the final Office Action, claims 1 to 3 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grotendorst et al. (U.S. Patent No. 5,408,040). This rejection is respectfully traversed.

It was maintained in the Office Action that Grotendorst et al. teach antibodies that would be specifically reactive with HBGF, as claimed, because some of the anti-CTGF antibodies of Grotendorst et al. would be expected to crossreact with HBGF. Applicants submit, however, that it is mere speculation that an anti-CTGF antibody would be specifically reactive with an HBGF polypeptide because the epitopes presented by HBGF would be expected to be substantially different from those presented by CTGF. As such, while an anti-CTGF antibody may have some relatively non-specific crossreactivity for HBGF, an anti-CTGF antibody would not reasonably be expected to be "specifically reactive" with HBGF as claimed.

It is well recognized that antibodies are raised against those portions of a polypeptide (i.e., epitopes) that are at the surface of the three dimensional structure formed by the polypeptide and, therefore, accessible to an antibody. The three dimensional structures of the epitopes presented by a polypeptide are dependent on the primary structure of the polypeptide, and the on the secondary and tertiary structures that result from the primary structure.

CTGF contains 349 amino acids, including 39 cysteine residues, which likely are involved in multiple intramolecular disulfide bonds, and 2 N-linked glycosylation sites at amino acids 28 and 225 (see Grotendorst et al., column 3, lines 41-60, and SEQ ID NO: 2). In comparison, the HBGF polypeptides contain about 100 amino acids, beginning at amino acid 247 or 248 of CTGF (see specification, Table 2, page 26), and, based on the sequence of CTGF, contain only 9 cysteine residues, and lack both of the N-linked glycosylation sites of CTGF (see Grotendorst et al., SEQ ID NO: 2).

It has long been recognized that a reference, to anticipate a claimed invention, must place the invention in the possession of the public. See, for example, In re Brown 141 U.S.P.Q. 245 (CCPA 1964); see page 249. With respect to the present invention, HBGF was not known prior

Applicants' disclosure in the subject application and, therefore, an antibody specifically reactive with HBGF could not have been known. It is submitted that the mere fact that an anti-CTGF antibody as described by Grotendorst et al. may have been specifically reactive with HBGF would not have been sufficient to apprise one of ordinary skill in the art of such antibodies. Thus, it is submitted that Grotendorst et al. do not anticipate the claimed antibodies because the reference does not place the claimed antibodies in the possession of the public.

In view of the substantial difference in the primary structure of CTGF and HBGF (i.e., 349 amino acids and about 100 amino acids, respectively) and the dependence of secondary and tertiary structure on the primary structure, particularly that associated with disulfide bond formation, it is submitted that it would have been mere speculation to suggest that the anti-CTGF antibodies of Grotendorst et al. would be specifically reactive with an HBGF polypeptide as claimed. Furthermore, the artisan would have recognized that CTGF can be N-glycosylated at one or two sites, whereas HBGF lacks the N-glycosylation sites of CTGF. As such, the artisan would have known that the anti-CTGF antibodies of Grotendorst et al. specific for an epitope comprising an N-linked carbohydrate residue, would not likely be specifically reactive with an HBGF polypeptide as claimed.

Nevertheless, in order to advance prosecution of the subject application, claim 1 has been amended to recite that an antibody, or antigen binding fragment thereof, of the invention is not reactive with CTGF (or with PDGF). In view of this amendment, it is submitted that the rejection over Grotendorst et al. is moot and, therefore, respectfully requested that the rejection of claims 1 to 3 under 35 U.S.C. § 102(b) be removed.

Claims 5 to 7 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over by Grotendorst al. in view of Hoogenboom et al. with respect to claims 6 and 7, or in view of Ladner et al. with respect to claims 5 and 6 . These rejections are respectfully traversed.

With respect to claims 6 and 7, it was stated that Grotendorst et al. describe anti-CTGF antibodies, some of which allegedly would bind HBGF. In combination with the Hoogenboom et al. reference, which describes humanized antibodies, it was alleged that the subject matter of claims 6 and 7 would have been obvious. However, for the reasons discussed above, and in view of the amendment to claim 1, it is submitted that Grotendorst et al. do not teach or suggest antibodies that are specifically reactive with HBGF as claimed. Since Hoogenboom et al. do not teach or suggest antibodies that are specifically reactive with HBGF, the reference does not provide that which is missing in the Grotendorst et al. reference. Accordingly, it is respectfully requested that this rejection of claims 6 and 7 under 35 U.S.C. § 103(a) be removed.

With respect to claims 5 and 6, it was stated that Grotendorst et al. describe anti-CTGF antibodies, some of which allegedly would bind HBGF. In combination with the Ladner et al. reference, which describes single chain antibodies, it was alleged that the subject matter of claims 5 and 6 would have been obvious. However, for the reasons discussed above, and in view of the amendment to claim 1, it is submitted that Grotendorst et al. do not teach or suggest antibodies that are specifically reactive with HBGF as claimed. Since Ladner et al. do not teach or suggest antibodies that are specifically reactive with HBGF, the reference does not remedy the failures of Grotendorst et al. Accordingly, it is respectfully requested that this rejection of claims 5 and 6 under 35 U.S.C. § 103(a) be removed.

In view of the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 2/2/01

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Enclosure: Exhibit A